REMARKS

Applicant respectfully requests reconsideration. Claims 1-3, 7-9, 26-30 and 33 were previously pending in this application. Claims 1-3, 7-9 and 26-30 remain pending, claim 33 is currently amended, with claims 1, 28 and 33 being independent. No new matter has been added.

Rejection of Claims 1-3, 7-9, 26-30 and 33 under 35 U.S.C. §103(a)

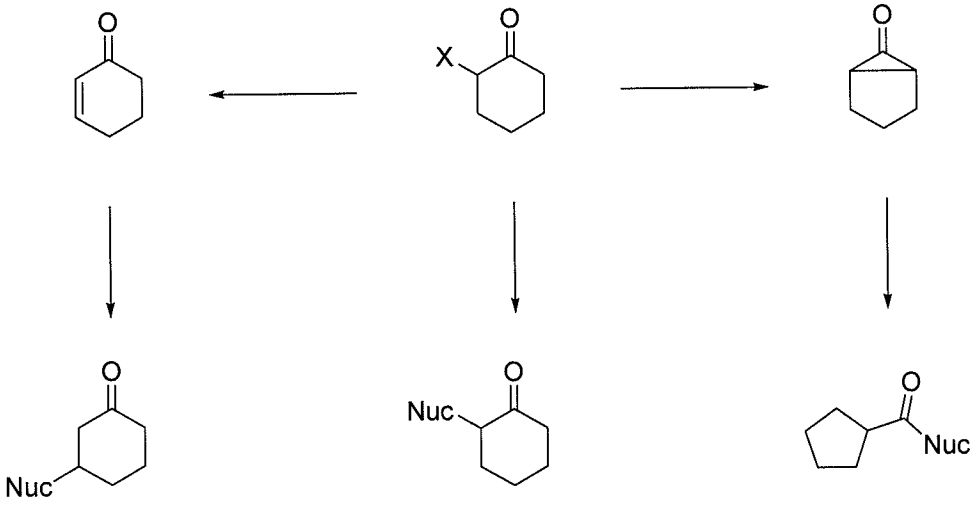
Claims 1-3, 7-9, 26-30 and 33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Leguzza in view of Solomons et al., Organic Chemistry, 2008, 9th Edition, John Wiley & Sons, Inc., page 224-236 ("Solomons"). At the outset, it is noted that Solomons is not properly prior art to the instant patent application which carries priority dates well prior to the publication date of Solomons. However, to expedite prosecution, Applicant addresses the rejection as presented, and addresses the aspect of the rejection attributable to Solomons only to the extent of the Patent Office's assertion that iodide is generally considered a better leaving group than bromide, with notice that in future prosecution Applicant may challenge the applicability of Solomons.

The Office Action states that an artisan of ordinary skill would have been motivated to make the alpha-iodoketone of the present invention in place of the alpha-bromoketone of Leguzza, because Solomons teaches that iodine is a better leaving group than bromine. The Office Action further states that one of ordinary skill in the art would have been motivated to convert the alpha-haloketone to the desired product to both increase the yield of the reaction and obtain the desired product via a more facile method having one less synthetic step than the process described in Leguzza.

Applicant sees no motivation or suggestion in Leguzza or Solomons to combine the teachings of Leguzza and Solomons in the manner stated in the Office Action. As noted in the response filed on December 15, 2008, one of ordinary skill in the art would not have been motivated to combine the teachings in the Leguzza patent with the teaching in Solomons in the manner stated in the Office Action. By contrast, those of ordinary skill in the art would expect that the use of iodine in the Leguzza process would produce an alpha-iodoketone that is highly unstable, relative to the corresponding alpha-bromoketone, increasing the risks of side reactions. Those of ordinary skill in the art would also expect that the alpha-iodoketone intermediate could not be isolated. Thus,

there would be no reasonable expectation of success in modifying the process of Leguzza with the teaching of Solomons.

For example, in a possible undesired side reaction, the alpha-haloketone could readily undergo elimination to leave an alpha,beta-unsaturated ketone (which itself could then undergo nucleophilic attack at the 'wrong' beta-position). As another example, under less acidic reaction conditions (e.g., relative to the conditions of the Leguzza process), the intermediate could also rearrange to yield a five-membered ring via a Favorskii rearrangement. This is particularly so for an alpha-iodoketone, which is more reactive than an alpha-bromoketone, as acknowledged in the Office Action. These possible side reactions are illustrated here:



Another possible difficulty with an increased reactivity of the alpha-haloketone is the presence of an amino group at the 4-position. This group not only inherently provides a base within the reaction mixture, but also has the potential to act as a competing nucleophile either inter- or intra-molecularly (*via* for example neighboring group participation with the C=C of the alpha,beta-unsaturated ketone).

On the basis of the above, although a more reactive intermediate may increase the rate of reaction, the number of possible side reactions that may occur is high. Accordingly, due to the greater number of possible unwanted reactions, those of ordinary skill in the art would believe that the most likely outcome would in fact be a reduction in the overall yield due to a relatively greater increase in the rate of formation or yield of at least one undesired reaction.

In addition, Applicant disagrees with the Examiner's assertion that there is not much of a yield difference between the process of Leguzza and the Applicant's claimed invention. The Office Action states that the yield for the compound N^6,N^6-dipropyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine•2HBr is 50%. Applicant fails to see how a yield of 50% is calculated. In contrast, Applicant believes the yield in Leguzza to be 27%, calculated as follows:

Moles of 4-di-*n*-propylaminocyclohexanone = (1 g)/(197.31 g/mole) = 0.0051 moles

Moles of 2-amino-5-di-*n*-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine•2HBr formed =

0.589 g (note: yield of purified compound)/(415.23 g/mole) = 0.0014 moles

% Yield of 2-amino-5-di-*n*-propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine•2HBr =

[(0.0014 moles)/(0.0051 moles)] x 100 = 27%

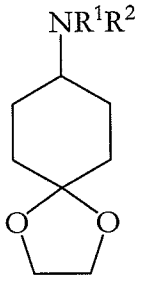
Thus, a significant increase in yield was obtained, from 27% to 56% (e.g., see paragraph [0060] of U.S. Patent Publication No. 2006/0106224), by substituting an iodoketone for a bromoketone. Such an increase in yield is highly significant and valuable on an industrial scale and represents a substantial improvement over the process of the Leguzza application.

A further unexpected advantage of the process of the present invention is that it allows the conversion to be performed *in situ*, i.e. without isolation of the alpha-haloketone intermediate. The process in the Leguzza application requires the use of glacial acetic acid, hydrogen bromide, and bromine. Those of ordinary skill in the art would be likely to expect a high risk of these reagents interfering with the cyclisation reaction with the thiourea if they were not removed. Accordingly, it follows that this is the reason the intermediate alpha-bromoketone was isolated in the process of the Leguzza application. In contrast, the use of iodine alone surprisingly resulted in reaction conditions that allowed for the halogenation of the ketone, yet were sufficiently mild to avoid substantial interference with the cyclisation process, therefore avoiding the need to isolate the alpha-iodoketone intermediate. Accordingly the process of the present invention may be performed in a much simpler manner than that of the process described in Leguzza, with consequent significant cost savings on an industrial scale.

Overall therefore it can be seen that the present invention is significantly higher yielding and more straightforward to perform than the process described in Leguzza.

Furthermore, the long time lapse (15+ years) between Leguzza and the filing date of the present application without any other reference disclosing the substitution of iodine for bromine in the process of Leguzza is further evidence of the inventiveness of this concept. Certainly, during this time period, much work had been done in the art to examine different synthetic routes to the products. Indeed, one aspect of the present invention is the realization that iodine could be used as a substitute for bromine.

With regard to claim 33, claim 33 has been made independent and recites a 4-amino-cyclohexanone-ethyleneketal having the structure:



2a ,

wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl. No where does Leguzza or Solomons teach or suggest this structure.

Because each claim limitation is not taught or suggested by Leguzza or Solomons, and there is no articulated reasoning as to why one of ordinary skill in the art would modify the teachings of Leguzza and/or Solomons to predictably reach the invention as claimed, claims 1, 28 and 33 are patentable over Leguzza and Solomons. Claims 2-3, 7-9, and 26-27, and claims 29-30 depend from claim 1 and claim 28, respectively, and, thus, are also patentable over Leguzza and Solomons, for at least this reason.

Accordingly, withdrawal of the rejection of these claims is respectfully requested.

CONCLUSION

If, for any reason, the Examiner is of the opinion that prosecution would be expedited via a telephone conversation with the Applicant's representative, the Examiner is kindly invited to contact the undersigned at (617) 646-8000.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

By _____

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